

Re: Amendment no. 3 of the protocol for the study "Serbian Smoking Reduction/Cessation Trial" (2SRT)

During the development of the Statistical Analysis Plan for the mentioned study, some inconsistencies, errors, or omissions have been detected in the protocol text. The purpose of this amendment is to correct these so that the protocol accurately reflects the study procedures and/or the intended purposes of the trial.

1. Randomization technique

p. 13, 3.3.3 Treatment assignment

Original protocol text:

"After providing informed consent at the baseline visit, the subjects will be randomly allocated to either active snus or placebo snus. Stratification will be made according to treatment centre. Randomization will be done by telephone to a central office where participant's identifiers are recorded. The random allocation will be done according to a computer-based algorithm"

Proposed amendment:

"After providing informed consent at the baseline visit, the subjects will be randomly allocated to either active snus or placebo snus. Stratification will be made according to treatment centre. *Randomization will be done by consecutively associating each included participant's identifiers with a unique, sequential number. A computer-based algorithm will generate these numbers in blocks of six for the two parallel treatment groups with equal probability: three to receive active snus and three to receive placebo snus. Lists at the study sites link the numbers to specific study products, that is, either active or placebo snus (in two sachet sizes and two flavours). At the sites all study products are identified solely by numbers to ensure the double-blinded study design. The procedures are described in more detail in the Randomisation Plan*".

2. Study products

p. 10, 3.1 Description of Overall Study Design and Plan, 3rd and 4th paragraph.

Original protocol text:

"The contents of snus and the placebo product are described in detail in an appendix to this protocol. The content of both products complies with the industrial standard GothiaTek.

It should be noted that the product used as the placebo in this trial is a snus replacement product that does not contain nicotine, but is widely marketed in Sweden under the brand name "Onico"

Proposed amendment: "

"The contents of snus and the placebo product are described in details in an appendix to this protocol. *The content of the snus products complies with the industrial standard GothiaTek which has been developed for smokefree tobacco products. As the placebo product does not contain tobacco, the GothiaTek standard is not applicable. However, the production of both snus and the placebo product accords with the Swedish Food Act.*

It should be noted that the placebo product does not contain *tobacco or nicotine*. An *almost identical product* is widely marketed as a *snus replacement product* in Sweden under the brand name “Onico”

3. Secondary outcome variables

p. 17, 2nd paragraph “Secondary Efficacy Assessment”

Original protocol text:

“Secondary efficacy assessments will be made at 12, 24, 36 and 48 weeks. Secondary end-points include

- “Smoking reduction” at 12 weeks
- Smoking cessation at 12 and 24 weeks defined as self-reported total abstinence from cigarettes during the preceding 4-week period verified by a concentration of CO in exhaled air of <10 ppm
- Smoking cessation at 36 and 48 weeks among those who achieved smoking reduction at 24 weeks (cessation here defined as self-reported total abstinence from cigarettes during the preceding 4, 12, or 24-week period, verified by a CO-concentration in exhaled air of <10 ppm at all measurements during the specified time period
- Clinical tests and biomarkers at 12 and 24 weeks among all participants, and at 36 and 48 weeks among those who achieved smoking reduction at 24 weeks including body weight, BMI, blood pressure, CO in exhaled air, measures of lung function (FEV1.0, FVC, FEV%), total S-WBC, S-CRP, total S-cholesterol, S-HDL, S-LDL, S-fibrinogen, S-cotinine”

Proposed amendment:

Secondary efficacy assessments will be made at 12, 24, 36 and 48 weeks. Secondary end-points include

- “Smoking reduction” at 12 weeks
- Smoking cessation at 12 and 24 weeks defined as self-reported total abstinence from cigarettes during the preceding 4-week period verified by a concentration of CO in exhaled air of <10 ppm
- Smoking cessation at 36 and 48 weeks among those who achieved smoking reduction at 24 weeks (cessation here defined as self-reported total abstinence from cigarettes during the preceding 4, 12, or 24-week period, verified by a CO-concentration in exhaled air of <10 ppm at all measurements during the specified time period
- Clinical tests and biomarkers at 12 and 24 weeks among all participants, and at 36 and 48 weeks among those who achieved smoking reduction at 24 weeks including body weight, BMI, blood pressure, CO in exhaled air, measures of lung function (FEV1.0, FVC, FEV%), total S-WBC, S-CRP, total S-cholesterol, S-HDL, S-LDL, S-fibrinogen, S-cotinine
- *Vital signs, body weight, and BMI at all clinical visits*